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GERALD K. WHITE
LAW FIRM OF GERALD K. WHITE & ASSOCIATES, P.C.
205 W. RANDOLPH STREET
SUITE 835
CHICAGO, IL 60606

EXAMINER	
GAMETT, DANIEL C	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/064,000	ELIA, JAMES P.	
	Examiner	Art Unit	
	DANIEL C. GAMETT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *403-405 and 407-412* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *403-405 and 407-412* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. In view of the Appeal Brief filed on 11/24/2008, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Manjunath N. Rao, /
Supervisory Patent Examiner, Art Unit 1647

2. Claims 403-405 and 407-412 are under consideration.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Rejection Claims 403-405 and 407-412 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained. Applicant's arguments filed 11/24/2008 have been fully considered but they are not persuasive. The rejection of record finds that the recitation in independent claim 403, step (b) "forming a bud" creates a lack of clarity as to whether the recited step requires action on the part of the practitioner of the method to form a bud. Applicant had previously argued that, "it is clear from the specification that the only step required by the practitioner is that of injecting stem cells into a selected site in a patient's body." (This argument is repeated in the instant Brief, p. 7). Thus, Applicant acknowledges that although step (b) (and, by implication, step (c)) has the form of a method step, the actual intent is to recite an intended outcome. The rejection of record finds that the claim defines the invention. Claim 403 still appears to recite a method step instructing the practitioner to form a bud. The office action mailed 05/05/2008 included the suggestion that the rejection could be overcome by an amendment to recite, "wherein the injected cells form a bud which grows to form an artery at said selected site, and wherein said artery integrates itself…"

5. Applicant now argues that "Examiner seems to be confusing the "definiteness" requirement of the second paragraph with the theory underlying Applicant's invention. The Examiner has not explained how an understanding of the underlying theory of the invention is required to render the claimed subject matter definite to one skilled in the medical art…. One skilled in the medical art would clearly understand and appreciate that organs, such as arteries, would grow in the body of a human patient from a bud primordium without further action by the practitioner." Applicant's argument seems to be directed toward a claim that recites "(a) locally

injecting stem cells into said body at said selected site, thereby forming a bud which grows to form an artery". Such language would clearly communicate that the act performed in step (a) is sufficient to cause a bud to form, and the practitioner of the method is not required to perform an additional act. Such an amendment would overcome the rejection with respect to step (b). The claim, however, recites "(b) forming a bud", which indicates that the practitioner is being instructed to do something. Likewise, the claim recites "(c) growing said desired artery from said bud", which also indicates that the practitioner is instructed to do something. This is not a question of one form of expression being preferred over another. The question of clarity first arises because the specification does not provide any teaching specifically directed to forming a bud. Furthermore, clarity on this is required in order to determine the relationship of the instant claim to the claims of copending application Serial No. 10/179,589. Applicant argues (Brief, p.37b) with regard to a provisional double patenting rejection, "It is pointed out that the claims in the instant application require the preliminary step of forming a bud in the body of the patient which then grows into an artery, while the claims co-pending application Serial No. 10/179,589 have no such requirement. Hence the claims presented in the respective applications are not drawn to identical subject matter." Applicant's argument regarding double patenting and argument against the rejection under 35 U.S.C. 112, second paragraph are mutually exclusive, they cannot both be persuasive. If step (b) instant claim 403 merely recites an inherent outcome of step (a), then step (b) cannot distinguish this claim from copending claim 161, which recites an identical step (a).

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Rejection of Claim 404 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record. Applicant's arguments filed 11/24/2008 have been fully considered but they are not persuasive. The rejection of record finds that claim 404, which first appeared in the record in the amendment of 11/03/2006, introduces new matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection finds no support for the combination of limitations that includes growing an artery by administration of stem cells to a damaged site in a leg of a patient in the specification as originally filed.

8. It is not the general concept of 'injecting stem cells' that is being rejected as lacking written description. Likewise, it is agreed that the specification provides support for the concept of growing an artery. The support for selecting these two species into a single method, i.e. 'injecting stem cells to grow an artery' is tenuous; this point has been made in the rejection of record, and it will be further addressed herein. Nevertheless, no claims that recite only "stem cell" and "artery" are under rejection as lacking written description. Rather, the rejection finds that the specific combination of limitations in claim 404 was not described in the specification as filed. While the support for selecting "stem cell" and "artery" into a single method is tenuous,

the concept of first combining these limitations and then further adding the limitation of placing the cell at a damaged site in a leg of a patient is non-existent.

9. Applicant submits (p11) that all the limitations of claim 404 appear in the specification as originally filed. Applicant further asserts (p.11) "The specification is replete with description of inserting a soft tissue growth promoter at a desired (damaged) site in the body (pages 10, 18, 20, 21, 31, 32, 45, 52, 53, 56, and 62)", and further that, "Appropriate compositions which promote the growth of soft tissue within the scope of Applicant's invention are described as comprising a patient's own cells (pages 47 and 48) and particularly stem cells (pages 37, 40, 41, 42, 48, 51 etc.) including autologous and allogeneic global bone marrow stem cells (bone marrow mononuclear cells/BMCs) and adult stem cells collected from peripheral blood." This precise argument appeared *verbatim* in Applicant's previous reply. Thus, Applicant has chosen to merely repeat the same argument, ~~rather than~~ rather than respond to the findings set forth in the office action mailed 05/05/2008, paragraphs 9-11, which included an analysis of each page of the specification cited by Applicant. It was first noted that when many of these same pages had been addressed in an earlier office action, Applicant responded by complaining that the "paragraph is gratuitously concerned with non-elected inventions and thus lacks focus upon the claimed invention". The rejection further found that pages 10, 18, 20, 21, 31, 32, 37, 40, 41, and 52 generically teach organs or tissues, but not the recited artery. Examples 15 and 16 (pages 41-42) suggest that stem cells from bone marrow or blood may be used to grow kidneys, not the claimed species of organ. Example 17 has a section directed to formation of an eye, but also includes a teaching (p.45) directed to artery formation which suggests "injecting a gene or other genetic material" (lines 2-3), VEGF genes (lines 10-11) or VEGF proteins (lines 13-15); no cells are

mentioned. Pages 47-48 mentions stem cells, among other cell types, and an artery, among other organs, but does not recite a damaged site in a leg. Example 18 (p.53) mentions legs, but teaches the use of recombinant DNA and does not reasonably suggest the use of any kind of cell to grow an artery. Examples 19 (p.55-56) and 35 (page 62) mention coronary arteries, not an artery in a damaged site in a leg, and like Example 18, Examples 19 and 35 teach the use of recombinant DNA and do not reasonably suggest the use of any kind of cell to grow an artery. Applicant's specification did not disclose with specificity which cells would or would not work for growing an artery. Cells are put forth for a variety of purposes. In some places it could be any cell. In others it is a skin cell that has undergone a mysterious process of dedifferentiation and redifferentiation. It might be a "germinal cell" "or in some cases stem cells". The cells are described as being "multifactorial and nonspecific", which does not provide any meaningful limitation as to the cells to use (see paragraphs 6-25 of the office action mailed 07/24/2007). Applicant has argued that one of skill would infer "stem cells" from sections of the specification that do not even mention any kind of cell. The combination recited in claim 404, requires the selection of "artery" from the genus of organs and soft tissues; selection of "stem cells" from the large genus of growth factors encompassed by Applicant's broad definition, and selection of a damaged site in a leg' from the genus of "the body". The specification does not suggest or contemplate the claimed combination. These teachings do not *reasonably* lead to the specific use of stem cells or the specific location in the leg, as required by claim 404. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species).

10. Applicant argues (p.14) that Examiner's reliance on case law relating to genus-species requirements misses the point and that the present Examiner is bound by his and prior PTO holdings. This was addressed on the record, specifically at paragraph 12 of the Final office action mailed 05/05/2008. It is first noted that Applicant's first reply in the prosecution of this case, filed 12/16/1999, dealt extensively with the scope of materials, including "growth factors", that can be used to grow soft tissue, but never once mentioned any kind of stem cell as having this capability. Claims reciting placing a "growth factor" into a body of a human patient were introduced into this application on 02/15/2001, which prompted a requirement for species election. Twenty-four patentably distinct species (a-x) of "growth factor" were found in the instant disclosure, from which Applicant was required to elect a single product or structure (requirement for restriction/election mailed on 02/24/2004). The list did not include "cells" or "stem cells" because "cells" or "stem cells" are never clearly set forth as species of growth factor anywhere in the instant specification. Cells (and certainly not stem cells) are not included in the definition of growth factor (specification pages 20-21). The expression "growth factors, such as stem cells" does not appear anywhere in the specification, it is never found in peer-reviewed non-patent literature, or in any patent literature, it only appears in arguments of counsel in this case and others with the same applicant. Use of the term "growth factor" to mean "cell" (or "cell" to mean "growth factor") is outside of the normal meanings of these terms. Applicant elected, without traverse, (03/03/2004) species a) "living organism", which was subsequently determined to include "cells". The notion that the specification aims to include "cells" within the genus of growth factors relies only on the fact that cells are, reasonably, "living organisms", which are listed as potential growth factors (specification page 20). While this line of reasoning

has been deemed sufficient to permit examination of claims that recite "cells" when the species "living organism" had been elected, it does not indicate that the PTO has held that a method of using stem cells for any particular purpose has been described. The point here is not that it is abhorrent or technically incorrect for the Applicant to attempt to define a class of growth factors that includes genes and bone marrow stem cells. The point is that any special meaning assigned to a term "must be sufficiently clear in the specification that any departure from common usage would be so understood by a person of experience in the field of the invention." *Multiform Desiccants Inc. v. Medzam Ltd.*, 133 F.3d 1473, 1477, 45 USPQ2d 1429, 1432 (Fed. Cir. 1998). The record is clear that the choice of "stem cell" as a species of growth factor was not an easy one to make; it involves first selecting "cells" from within an enormous genus of asserted growth factors, and then selecting "stem cells" from within the genus of cells. This is only one of the selections that must be made to arrive at claim 404.

11. In *Purdue Pharma L.P. v. Faulding Inc.*, 230 F. 3d 1320, 1326, 56 USPQ2d 1481, 1486 (Fed Cir. 2000), the court noted that with respect to *In re Ruschig* 379 F.2d 990, 154 USPQ 118 (CCPA 1967) that "Ruschig makes clear that one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say here is my invention". In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure." To arrive at the combination recited in claim 404, requires the selection of "artery" from the genus of organs, selection of "stem cells" from the large genus of growth factors encompassed by Applicant's broad definition, and selection of "damaged site in a leg" as the site where the artery is to be grown. Applicant has correctly pointed out that to comply with the written description requirement of 35 U.S.C. 112, first

paragraph, 'the applicant must.., convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.' Vas-Cath, 935 F.2d at 1563-64, 19 USPQ2d at 1117. One cannot ignore *reasonable clarity*. The mere presence of all of the limitations at various locations in the specification does not constitute adequate written description. The specification as filed does not contemplate the claimed combination of limitations. Taken as a whole and in view of Applicant's cited pages therein, the specification does not reasonably lead the skilled artisan to the recited combination of the agent to be administered, the desired result, and the site of administration. Even if one of skill in the art could infer the claimed method by combining the disconnected teachings of the specification, at best this would only render claim 404 obvious in view of the specification. Disclosure which merely renders the later claimed invention obvious is not sufficient to satisfy the written description requirement of 35 U.S.C. 112, first paragraph. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1505, 41 USPQ2d 1961 at 1966. The introduction of this combination of limitations in claim 404 in the amendment filed 11/03/2006 involves narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure, which is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. Therefore the introduction of this combination of limitations in claim 404 in the amendment filed 11/03/2006 constitutes new matter.

12. Rejection of Claims 403-405 and 407-412 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for reasons of record. Applicant's arguments filed 11/24/2008 have been fully considered but they are not persuasive. The rejection

of record has found that *the breadth of the claims* and the *amount of direction or guidance present and the presence or absence of working examples* are the principle factors that speak against the enablement for the claims under consideration. The breadth of the claims as currently amended is considerably narrowed in reciting a single organ, an artery, and a subgenus of cells, stem cells. The latter subgenus is still large, however, as the term "stem cell" includes embryonic stem cells, neural stem cells, amniotic epithelial cells, hematopoietic stem cells, and mesenchymal stem cells, to mention those cited in references of record. Therefore, the question of which cells would or would not work for growing an artery is critical to breadth of the claims and to enablement of the general methods. As noted previously, even if interpreted in Applicant's most favored light, the most precise description of the cells to be administered in the instantly claimed methods is "bone marrow stem cells". Thus, the breadth of the term "stem cell" cannot not be supported by an enabling disclosure. The remaining arguments presented herein are directed to the arguments presented in Applicant's Appeal Brief, filed 11/24/2008.

13. It is first noted that Applicant has separately argued claims 403, 411, and 412, claims 404 and 405, and claims 407-410. The rejection of record finds that elements that are essential and common to all of the claims are not enabled by the disclosure. No recited limitation rescues any claim from lack of enablement. Therefore, this office action will provide a single rejection and response to all of 403-405 and 407-412.

14. The rejection of record finds that the instant specification did not disclose with specificity which cells would or would not work for growing an artery. Applicant asserts (p.17) that the instant specification describes "a class of claimed and unclaimed growth factors that broadly and specifically include genes, nucleic acids, a patient's own cells (autologous cells), or universal

cells, e.g., stem cells (global mononuclear bone marrow cells), etc., all of which are described to promote tissue growth through differentiation and morphogenesis." This disclosure is said to provide "a scope of enablement which includes stem cells broadly (pages 37, 48, 50, and 51) and bone marrow mononuclear stem cells specifically (pages 40-42). Such disclosure is commensurate in scope with the subject matter of the claims at issue." Similarly, Applicant argues (p. 18) "One skilled in the art reading the instant specification's teaching of using stem cells harvested from the bone marrow or blood of the patient would understand that the claimed invention distinguishes from Isner '887 by describing using unfractionated (global) bone marrow mononuclear cells." On page 25, Applicant argues, "One skilled in the art reading the subject specification would clearly understand that Appellant was in possession of the concept of implanting whole (unfractionated) bone marrow mononuclear cells to promote growth of organs, such as arteries, in a human patient." Applicant argues (p.24) that "Appellant's contribution to the art resides in the discovery that unfractionated bone marrow stem cells, through differentiation and morphogenesis, form an organ, i.e., an artery, when locally implanted in a body."

15. These arguments are not persuasive for the following reasons. First, the arguments are directed to limitations that are not in the claims. While claim 407 recites a stem cell harvested from bone marrow, none of the claims under consideration recites unfractionated (global) bone marrow mononuclear cells. If such claims were to be presented, they would be properly rejected because the specification does not even disclose the concept of using unfractionated bone marrow mononuclear cells, let alone teach a method of using them. The instant specification does not teach that there is anything critical about how to prepare bone marrow stem cells. The

specification does not mention any requirement or criticality of using "unfractionated (global) bone marrow mononuclear cells". None of the terms "unfractionated", "global" or "mononuclear" are used, even once, in the specification. The instant specification refers to bone marrow only in the sentence, "Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques", which appears three times (page 40, lines 27-28; page 41, lines 23-24; page 42, lines 9-10). "Stem cells harvested from cell culture techniques" are not equivalent to "unfractionated (global) bone marrow mononuclear cells". The expression "stem cells harvested from cell culture techniques" does not even limit the original source to bone marrow. "Stem cells harvested from the blood of the patient" are not equivalent to "unfractionated (global) bone marrow mononuclear cells". The expression "stem cells harvested from the blood of the patient" actually teaches away from "unfractionated (global) bone marrow mononuclear cells". If indeed Applicant's contribution to the art resides in the discovery that unfractionated bone marrow stem cells, through differentiation and morphogenesis, form an organ, i.e., an artery, when locally implanted in a body, then Applicant should have written a specification that describes that contribution.

16. "Unfractionated (global) bone marrow mononuclear cells" would *include* stem cells, but the expressions "stem cells harvested from the bone marrow" and "unfractionated (global) bone marrow mononuclear cells" are not equivalent. The expression "unfractionated (global) bone marrow mononuclear cells" necessarily includes all of the bone marrow mononuclear cells, not just stem cells. At the time the instant application was filed, the expressions "stem cells harvested from the bone marrow" and "stem cells harvested from the blood" were typically understood to refer to the CD34+ fraction (Rowley *et al.*, Bone Marrow Transplantation, June

1998, Volume 21, Number 12, Pages 1253-1262; see p. 1253, first three sentences of Summary and top of right column). The instant specification does not indicate that any other meaning was intended. In the case of cells harvested from blood, it was still unclear long after the instant specification was filed whether circulating blood contains any mesenchymal stem cells or other marrow-derived cells with broad potential (Roufosse *et al.*, Int J Biochem Cell Biol. 2004 Apr;36(4):585-597; see especially section 3, pp. 588-591, Table 2, and section 6, p. 394). Isner '887 made the discovery that the CD34+ mononuclear cell population, present in both bone marrow and peripheral blood, comprises progenitors for endothelial cells as well as the previously identified hematopoietic progenitors. Applicant has raised doubt as to whether the endothelial progenitors described in Isner '887 can actually form an artery, as opposed to merely integrating into capillary wall. However, post-filing references of record do show that cells derived from bone marrow are able to stimulate neovascularization. It was previously established in the record that the precise population of cells that gives rise to the endothelial progenitors described by Isner, and well as the cells identities of the bone marrow cells that stimulate neovascularization remains uncertain, as is, at least until as recently as the Rabelink 2004 reference of record (see the office action mailed 05/05/08 at paragraph 27). The population of bone marrow mononuclear cells used by Strauer (2002, of record) comprised only 2.1% CD34-positive cells (Strauer, p. 1914, paragraph bridging the columns). Similarly, the Kornowski '832 patent explicitly proposed that the use of cells per se could provide a sustained source of angiogenic agents, and refers to "bone marrow" and to "the cells" in bone marrow, but not specifically to the *stem cell* population from bone marrow (column 4, lines 45-49). Kornowski discloses that cellular infiltrates in tissue after administration filtered bone marrow aspirates were 4-6% CD34+ (column 13, line 43-45). It is evident from Stauer and Kornowski that the critical cell in the preparations they administered may not be any

previously characterized stem cell; it may not even be a *stem cell* at all but rather some other previously uncharacterized growth factor secreting cell. The instant claims require a stem cell. Claim 407 and its dependents require a stem cell harvested from bone marrow. Claim 409 and its dependents require a stem cell harvested from blood. Therefore, the '887 and '832 patent disclosures and the Stauer and Rabelink references represent subsequent experimentation that reveals factual uncertainty which "so undermines the specificity of the inventor's idea that it is not yet a definite and permanent reflection of the complete invention as it will be used in practice." See Burroughs Wellcome Co. v. Barr Labs., Inc., 40 F.3d 1223, 1229, 32 USPQ2d 1915, 1920 (Fed. Cir. 1994), It is further evident that the concept of using unfractionated bone marrow mononuclear cells comes from Strauer and/or Kornowski, not the instant specification.

17. Applicant states (p.23) that "The Examiner at pages 15-17, ¶20 of the Final asserts that the instant specification fails to provide any guidance as to how to use any kind of cell, much less a stem cell, to grow an artery. The disclosure at page 47, line 22 through page 48, line 15 of the specification clearly rebuts the Examiner's notion that Appellant never clearly enunciated using stem cells (bone marrow stem cells) for promoting direct differentiation and morphogenesis into an organ. Of course, one skilled in the art would recognize that growth of an organ encompasses an artery." The Examiner cannot find the exact quote in paragraph 20, which began on page 13, or anywhere on pages 15-17 of the Final action mailed 05/05/2008. Nevertheless, the Examiner acknowledges having written something like, "the instant specification fails to provide any guidance as to how to use any kind of cell, much less a stem cell, to grow an artery" at some point in the prosecution of this or a related case. In response, it is first noted that Applicant first asserts that the specification "clearly enunciated using stem cells

(bone marrow stem cells) for promoting direct differentiation and morphogenesis into *an organ*" (emphasis added). Of course growth of an organ encompasses an artery. Growth of an organ can also encompass growth of pancreatic islet cells or a heart (specification p.48, lines 3-4). Elsewhere, the specification mentions growth of a tooth, a kidney, or an eye. If stem cells can do all of these things, how does one control the process to specifically form an artery? Simply *enunciating* using stem cells for promoting direct differentiation and morphogenesis into *an organ* does not teach one of skill in the art *how to* grow *an artery*. Applicant's disclosure at page 47, line 22 through page 48, line 15 of the specification has been thoroughly addressed in the record. See, for example, the Final rejection mailed 05/05/08 at paragraphs 29-32, which finds that the specification tosses out the idea that something can be done and then invites the skilled artisan to figure out how to do it.

18. Further related to the guidance in the specification as to how to use stem cells to form an artery, Applicant argues (p. 27) that, "It is clear from Isner '887 that stem cells home to foci of injury. Accordingly, one skilled in the art reading the subject specification would understand that all that is required to use pluripotent stem cells to grow an artery is to implant them at the desired site." As noted above, Applicant has argued that the cells disclosed in Isner '887 are distinct from the stem cells recited for use in the instant claims. For example, Applicant asserts on p. 14, "Isner '887 differs from the present invention by disclosing and claiming injecting endothelial progenitor cells that are necessarily limited to promoting endothelial cell growth (capillary blood vessels), not artery growth as required in instant claim 404". The specificity with which the instant application teaches the use of any stem cell population to grow an artery is under dispute, as detailed elsewhere. Here, the point is that Applicant is asserting contradictory weight to the

Isner '887 patent. If, as Applicant asserts on p. 14, Isner '887 discloses a progenitor cell population that is distinct from the cells recited in the instant claims, how then can it be assumed that Isner '887 would cause one of skill in the art to know that all that is required to use the allegedly distinct stem cells of the instant claim to grow an artery is to implant them at the desired site?

19. Applicant states on p. 26, "The Examiner's charge at pages 21 and 22, ¶25 of the Final that Appellant is practicing obfuscation by taking language from different portions of the text in order to support the claimed language is disturbing indeed." The Examiner agrees that this is disturbing, but the facts are on the record. To review, Applicant's response filed 11/28/2007 included the following on page 18:

> The art skilled is told that "reimplanting" a "patient's own stem cells results in differentiation and morphogenesis of a organ, i.e., artery, in a human patient."

20. The quotation marks in the original were exactly as reproduced above. Thus, the reader of this sentence is lead to believe that the specification contains a phrase that says exactly, "patient's own stem cells results in differentiation and morphogenesis of a organ, i.e., artery, in a human patient." The Examiner sought to set the record straight in paragraph 29 (not 25) of the office action mailed 05/05/2008. It was found that the specification does not contain the phrase "patient's own stem cells results in differentiation and morphogenesis of a organ, i.e., artery, in a human patient." The words within the quotation marks were formed by joining parts of sentences from separate paragraphs in an apparent attempt to make it appear that the teaching in the specification is more explicit than it actually is. Two source sentences were identified: "In the example above, if germinal cells (and in some cases, stem cells) are utilized a ([sic] to?) direct

differentiation and morphogenesis into an organ can occur in vivo, ex vivo, or in vitro", from page 48, lines 13-15, and "A cell nutrient culture may or may not be utilized depending on the desired functional outcome (**i.e., growth of an artery**, of pancreatic Islet cells, of a heart, etc.) or other circumstances", from page 48 lines 2-4. Upon further inspection, it is evident that at third sentence is involved: "Organs and/or tissues can be formed utilizing the **patient's own cells**, from page 47, line 22). The Examiner, being familiar with the case, might consider this as mere argumentation aimed at joining the concepts from contiguous paragraphs in the specification. However, a reviewer, such as for example, a judge on the Board of Patent Appeals and Interferences, or a higher court, could read Applicant's sentence and be lead to believe that the specification actually contains the phrase in quotes, and thereby receive an erroneous impression of what the specification actually says. Applicant has stated on page 27, "Perhaps, the Examiner needs to be reminded that the PTO examination process is not an adversarial proceeding." The Examiner agrees that the PTO examination process is not *supposed to be* an adversarial proceeding. However, a tactic of joining parts of sentences from separate paragraphs and presenting the composite sentence as if it were a quote from the specification, in an attempt to make the specification appear to provide more explicit teaching than actually is present will not go unchallenged.

21. Turning to the argument on page 26 regarding the content of page 47, line 22 through page 48, line 15 of the specification, it is first noted that Applicants assertion that the analysis "artfully omits the following two paragraphs…" is not true with respect to "In the example above, if germinal cells (and in some cases, stem cells)are utilized a direct differentiation and morphogenesis into an organ can occur in vivo, ex vivo, or in vitro" (specification, page 48, lines

13-15)—this was quoted in its entirety in paragraph 29 of the office action mailed 05/05/08. Applicant argues that when read in its proper context by one skilled in the medical art, the language on page 48, line 13 of the specification "[i]n the example above..." refers to the formation (page 47, line 22) of "[o]rgans and/or tissues...formed utilizing the patient's own cells." The rejection of record is not entirely in disagreement with this interpretation, with the proviso that an interpretation that requires reading in context to piece the concept together is not so explicitly clear as if the specification had actually contained Applicant's fictitious phrase "patient's own stem cells results in differentiation and morphogenesis of a organ, i.e., artery, in a human patient." Furthermore, the rejection of record also finds "even if "In the example above, if germinal cells (and in some cases, stem cells) are utilized a direct differentiation and morphogenesis into an organ" (specification p.48) is taken to mean that stem cells are to take the place of the skin cells or germinal cells of the example, so that use of stem cells to grow an artery is "contemplated"… it does not even begin to teach one of skill in the art how to use stem cells to grow an artery." For reasons given in detail in paragraph 31 of the office action mailed 05/05/08, page 47, line 22 through page 48, line 15 (the parts eliminated from Applicant's composite sentence) of the specification generally points toward some of the complex problems that might be encountered in regenerative medicine (choosing the right cell type, the possibility of preexisting genetic damage in the cells, the multiple factors that may direct pluripotent cells to differentiate in specified pathways) but does not teach the skilled artisan any solution to these problems. The specification tosses out the idea that something can be done and then invites the skilled artisan to figure out how to do it.

22. On page 27, Applicant states that "The Examiner's statement at page 25, ¶30 [*sic* 33?] of the Final lacks merit, but none-the-less is disconcerting. Appellant has continuously argued and cited legal authority supporting the proposition that the entire specification disclosure must be considered by the PTO when determining whether the scope of the claimed subject matter on appeal reasonably finds descriptive and enabling support therein. However, such argument does not open the door to the Examiner's gratuitous and sometimes derogatory expressions of opinion concerning unclaimed inventions." Applicant is apparently referring to paragraph 33: "Lest Applicant should argue that the discussion of such topics as DNA repair, genetic fitness, dedifferentiation, redifferentiation, cell nutrient culture, and the vagueness of the term "germinal cells" are "gratuitously concerned with non-elected inventions and thus lacks focus upon the claimed invention", Applicant is reminded that Applicant has repeatedly asserted that the entire disclosure should be read and considered." As noted above, paragraphs 29-32 had included an analysis of page 47, line 22 through page 48, line 15 of the specification. Paragraph 33 was meant to emphasize that paragraph 29-32 were not "gratuitously concerned with non-elected inventions" nor did they lack "focus upon the claimed invention". Page 47, line 22 through page 48, line 15 of the specification had been cited by Applicant as providing support for the claimed invention. It is, therefore, altogether fitting that an analysis of what this section of the specification *actually says* should be made of record. The specification actually suggests the examination of fitness of unknown genes by unidentified criteria, the use of unidentified machines, unknown methods of effecting DNA repair, the addition of unknown and undefined growth factors, ECM components, nutrients, and/or vitamins to cause cells to undergo dedifferentiation, redifferentiation, and morphogenesis into *any desired organ or tissue*, and

unidentified "germinal cells". These teachings are found to be inadequate for guiding the skilled artisan to grow an artery.

23. In a similar vein, Applicant has stated on p. 23 "Hubris aside, the rhetorical theme employed by the Examiner at pages 15-17, ¶20 of the Final appears to lack proper decorum." Applicant appears to be referring to paragraph 23, which began on page 15 and ended on page 17 of the office action mailed 05/05/2008. Here again, the rejection provided an analysis of pages of the specification that Applicant has specifically and repeatedly cited as supporting the description and enablement of the instant claims (For examples, see pages 11 and 17 of the instant Appeal Brief). It is, therefore, altogether fitting that an analysis of what these pages of the specification *actually say* should be made of record. *Applicant identified* pages in the specification as providing support for the claims. The Examiner accurately reported the contents of those pages and concluded that not one of them teaches one of skill in the art how to use any kind of cell to grow an artery. If the analysis seems to be "concerned with non-elected inventions" or to "lack focus upon the claimed invention", well, that is the point—the pages do not even mention growth of an artery. It is noted that *the pages under discussion contain the only mentions of stem cells harvested from the bone marrow in the entire specification*. The fact that certain teachings on the pages *Applicant chose* for discussion can be accurately described as "fantastic speculation", "nonsensical", or "does not set forth a credible procedure to produce the asserted results" is relevant to the enablement issue under discussion. The skilled artisan is required to ignore these teachings, but then look to the remainder of the specification for guidance in a novel method. These teachings are part of the "specification as a whole" that Applicant repeatedly urges should be considered. Applicant apparently believes that the skilled

artisan should take from these pages only the fact that they mention "cells" and "organs" but then ignore what they *actually say* about which cells to use, which organs to grow, or how to perform methods of using the cells. It is noted that Applicant has not challenged the facts or tried to say that the specification was inaccurately presented in paragraph 23 of the office action mailed 05/05/2008. Applicant apparently simply wishes that these facts would not be discussed. Proper decorum does not require that the Examiner cooperate with Applicant in keeping the weaknesses of the specification off the record. Applicant is advised that if Applicant persists in asserting that sections of the specification support description or enablement of the claims under consideration, the *actual content* of those pages will be discussed in detail on the record.

24. Applicant addresses (pp.27-31) the question of extrapolation of dosages of a VEGF cDNA construct taught in Example 18, to calculate a number of stem cells to use in a method wherein stem cells are used in place of the cDNA construct. Appellant submits it is clear from MPEP Section 2164.01 (c) that it is not necessary to specify the dosage if one skilled in the art could determine such information without undue experimentation. The Examiner agrees that, by itself, the presence or absence guidance as to how many stem cells should be used to grow an artery would not answer the question of whether the instant disclosure satisfies the requirements of 35 U.S.C. 112, first paragraph. The rejection, as originally set forth, did not specifically mention the absence of guidance as to how many stem cells should be used to grow an artery. However, if present, a recommended dosage would be understood as guidance to be considered along with the other factors in the enablement analysis. Applicant has attempted to show that such guidance is present in the specification. Applicant argues that Example 18, not only suggests the use of stem cells to grow an artery, it provides guidance in the number of cells to use, because one of skill would

extrapolate an appropriate cell number from the quantities of plasmid DNA taught in the Example. No such extrapolation is taught the instant specification as filed. A specific method for making this extrapolation was first entered the record in this case only as Exhibits D of the Lorincz and Heuser declarations filed on 05/25/2007. Therefore, this extrapolation is only under discussion because Applicant apparently seeks to establish that an extrapolation of this type is so well known in the art that it would be implicitly understood to be present in example 18 of the specification.

25. Applicant asserts that, "Appellant used a well established weight basis conversion method employed in the medical art for decades to convert the gene dosage of Example 18 to cells." This is not true, as demonstrated in the record. The conversion charts and methods that Applicant cites as having been employed in the medical art for decades are methods wherein *an amount of cellular DNA is used to calculate a number of cells of the same species as the source of DNA*. This is demonstrated in the Declarations filed 05/25/2007 by Drs. Heuser and Lorincz. The Declarants based their statements on the fact that cellular DNA contents are constant within a species; examples were given wherein DNA in a blood sample was used to calculate the number of nucleated blood cells in the sample. In the Declarations filed 05/25/2007, Drs. Lorincz and Heuser concluded that the conversion depicted in Exhibit D is *consistent* with the extrapolations that have been performed for over 50 years. This carefully worded conclusion is not challenged. It, remains undisputed, however, that the consistency extends only to the point that the extrapolations involve math and DNA; any further comparisons would be impossible. Unlike the "well established weight basis conversion method" Applicant refers to, the extrapolation under discussion attempts to convert *an amount of a plasmid DNA construct to a number of stem cells*.

Plasmids are found natively in bacteria, not human stem cells. Therefore, the conversion under discussion is fundamentally different from the extrapolations discussed by the Declarants, because it crosses species lines. Furthermore, a *plasmid DNA construct* is designed to express a single desired gene, which is quantitatively and qualitatively different from genomic DNA as it is found in cells. Every molecule of the postulated plasmid DNA comprises a copy of the VEGF cDNA. In contrast, VEGF coding sequences would comprise but one of 30-40 thousand genes in genomic DNA (at the time of filing, it was widely believed that the human genome comprised 100,000 genes). Isner et al., (*Circulation.* 1995; 91:2687-2692; of record) describe construction of the plasmid phVEGF$_{165}$, which appears (without attribution) to be the model for the plasmids mentioned in the specification. According to Isner *et al.* phVEGF$_{165}$ consists of a total of 5651 bp (base pairs). Of these, 3,162 bp are from pUC118, 763 bp are the CMV promoter/enhancer, and 1726 bp are VEGF cDNA. Therefore, the plasmid has one copy of VEGF coding sequences per approximately 5.7 kb (kilobase pairs). According to the data supplied by Drs. Lorincz and Heuser, in the table labeled "II. Some useful nucleotide dimensions", humans have 3×10^9 base pairs per haploid genome. This converts to 3×10^6 kb. Assuming 1 VEGF gene per haploid genome, 3×10^6 kb of human genomic DNA contains the same number of VEGF genes as 5.7 kb of the plasmid phVEGF$_{165}$. Therefore, the amount of VEGF coding sequence in an equal mass of human genomic DNA and VEGF plasmid DNA differs by a factor of 5.26×10^5. Inclusion of placental growth factor (PlGF), VEGF-B, -C, and –D as "VEGF genes" in genomic DNA would reduce this factor to about 1×10^5. Therefore, it is fundamentally illogical to equate recombinant plasmid DNA to cellular DNA on the basis of mass. See also the office action mailed 07/24/2007 at paragraph 38, which established that scientists 50 years prior to the filing date of

the instant application (a time period cited in the Declarations filed 05/25/2007 at paragraph 6) would not recognize the terminology or even imagine the concept of the conversion depicted in Exhibit D. It is, therefore, impossible for Applicant's statement that "such extrapolations have been used for decades in the medical arts in regard to cell therapy" to be true. All of this has been presented to Applicant in previous office actions. Applicant has declined to present an argument to refute this.

26. Applicant asserts to have based the extrapolation calculation on the teaching is Isner '887. Isner teaches, "The effective dose of the nucleic acid will be a function of the particular expressed protein, the target tissue, the patient and his or her clinical condition. Effective amount of DNA are between about 1 and 4000 μg, more preferably about 1000 and 2000, most preferably between about 2000 and 4000", and "Generally, from about 10^6 to about 10^{18} progenitor cells are administered to the patient for transplantation" (column 11, lines 4-9 and column 7, lines 17-23, respectively). Using these values, and an assumption of 40 pg of genomic DNA/cell, Applicant arrives at a number of cells that is within the *trillion-fold range* taught in Isner (footnote, pp. 28-29). There is no evidence that Isner ever used the plasmid DNA values to arrive at the cell values. It is noteworthy that the Isner '887 patent cites inventor Isner's earlier work using a VEGF plasmid to indicate feasibility of gene therapy for modulating angiogenesis (col. 2, lines 19-23). If amounts of plasmid DNA were routinely usable as a guide to the number of cells to use, one would think the inventor Isner, an acknowledged expert in both gene therapy and cell therapy, would have mentioned it. However, nowhere does the '887 patent suggest that the amount of plasmid DNA was used as a guide for the amount of cells to use in the pioneering cell therapy disclosed in the patent. Isner, in fact, discusses shortcomings of plasmid-based gene

therapy, pointing to a need for means to more precisely regulate angiogenesis at a given location (col. 2, lines 24-35). It is clear from the '887 patent that inventor Isner viewed gene therapy and cell therapy as distinct methods, each with its own advantages, disadvantages, and technical features. Thus, Isner '887 stands in distinct contrast to Applicant's assertion (p.29), "The Examiner's statement at pages 27 and 28 of the Final that a person of skill in the art "...would never attempt such an extrapolation" is based on the incorrect determination that implanting genes is a technically different process from implanting cells." If inventor Isner did not see guidance for the number of cells to use in cell therapy in his own work with gene therapy, why would any person of skill in the art draw the opposite conclusion by reading the gene therapy examples in the instant specification, which in fact were derived (without attribution) from Isner's published work?

27. Applicant has denied that the calculation in question should be referred to as "Applicant's formula" (Brief, p. 30). Curiously, after this denial Applicant made reference to "Appellant's conversion" in the very next paragraph (p.30). It is clear, however, from the facts presented herein and in the rejections of record, that the method is indeed Applicant's post hoc derivation. It is not implicit in the teachings of the specification. It is not substantially analogous to well known methods of converting DNA amounts to cell numbers within a species cited by the Declarants. There is no rational basis for proposing that a person of skill in the art at the time the instant application was filed would even think of doing it without being specifically prompted to do so. The instant specification does not provide that prompting. If, as Applicant contends, the use of the amount of recombinant plasmid DNA in a gene therapy protocol to calculate the number of stem cells to use in a cell therapy procedure is well known in the art, then numerous

examples of extrapolations like the one in question should easily be found in the peer-reviewed scientific literature or the patent literature. Such an example would refute the Examiner's position more certainly than any carefully worded Declaration that cites a "consistency" between calculations. Applicant has not provided any such example. Therefore, Applicant cannot claim that Example 18 of the specification provides guidance, or even any suggestion, in the use of stem cells to grow an artery.

28. Beginning at page 31, Applicant addresses the issue of actual working examples in the specification. Applicant asserts, "The *armamentaria* underlying the Examiner's rejection is a requirement for actual clinical testing in order for inventions in the medical field to satisfy the enablement requirement of the statute." This mischaracterizes the rationale for the rejection. In fact, the rejection explicitly stated, "First, the USPTO cannot, and does not, demand human clinical trials to demonstrate enablement for claims to methods of treating humans. Nothing in the rejections of record can logically be taken to imply such a demand" (paragraph 400, p. 31 top).

29. The most Applicant can say about the instant disclosure is that, by circuitous logic not explicitly presented in the disclosure, one of skill in the art might surmise that a method to use autologous stem cells to grow an artery was suggested. For example, upon reading juxtaposed excerpts of the specification (not the complete specification), the Declarants of record have been willing to say: "The disclosures referenced in above Paragraph ... of the specification *relate to* using a growth factor for promoting the growth of soft tissue, and more specifically, to a method of using a cell, *such as* a stem cell, to grow soft tissue, *such as* an artery" (emphasis added)." With regard the enablement requirement, the appropriate factual determination is whether the

instant specification reasonably directs one skilled in the art how to *make and use* the claimed subject matter. A disclosure that makes it is possible to piece the claimed generic concept together is not the same as an enabling disclosure. As was found in *Ex parte Hitzeman*, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present specification does not disclose even a single enabled embodiment of the claimed method. The instant specification does not show a single organ, part of an organ, tissue, artery, or even a bud formed by placing cells in a body. Thus, Applicant's assertion (p.19) that "the materials and administration techniques, but not the inventive results, were well known when the instant application was filed" is not persuasive: There are no inventive results. Applicant has admitted that a specification should "specify embodiments that work" to satisfy the enablement requirement (p. 25). The instant specification does not meet this requirement.

30. On page 33, Applicant comments, "The Examiner, at pages 30 and 31 of the Final, stated that the PTO is forbidden to comment upon the validity of Isner '887, but then curiously proceeded to apparently defend the validity of this patent. Lest there be any misunderstanding, Appellant has never stated that Isner '887 is invalid." Here, Applicant seems to have missed the point, or is perhaps attempting to divert attention from the point, made in the cite section of the office action. Applicant had previously alleged having received "extra statutory/regulatory

negative responses". According to Applicant, the issued Isner '887 and Kornowski '832 patents indicate that Dr. Elia's improvement to the medical arts has fostered prejudicial skepticism because of its manner of reduction to practice. To respond to this allegation, it was necessary for the Examiner to discuss details in the issued patents. In so doing, the Examiner was careful to disclaim any intent to comment on the validity of the patents. This was not meant to imply that Applicant had called the validity of the patents into question. The points made in the rejection, from which Applicant has attempted to divert attention, are as follows. The Isner '887 and Kornowski '832 patents illustrate that patents in which biotechnological inventions are directed to the treatment of humans rely on animal, or even in vitro, evidence that the claimed methods are supported by a sound scientific basis, that the methods can work, and to provide enough guidance so that application to humans can proceed with a reasonable expectation of success. The examples in the patents are not human clinical trials, but neither are they prophetic, as Applicant had alleged. The instant specification provides no comparable evidence upon which to base a judgment. Thus, the Examiner did not aim to defend the validity of the allowed patents, but rather to explain how the deficiency of the instant disclosure contributes to the instant rejection.

31. Also on page 33, Applicant states, "Appellant never, intentionally or unintentionally, linked an absence of an art rejection with proof of enablement." The record shows otherwise. In Applicant's remarks filed 04/30/2007, the following can be found bridging pages 36-37:

> "Such statement evinces a total misunderstanding on the part of the Examiner in regard to the manner in which the Court applied "the state of the art" factor in In re Wands. Simply put, if the prior art had taught Applicant's invention, the parties would not be at this point in the instant prosecution. As evidenced by the Examiner's failure to reject the claims on prior art, this is not the situation at hand."

32. Finally, on page 35-36, Applicant argues that any *prima facie* case of lack of enablement has been rebutted by the submission of the multiple Declarations of experts in the medical field. This is not persuasive. The Declarations and the weight given to them have been addressed in the record. Declarations have been addressed herein, and for example, in sections 34-38 of the office action mailed 05/05/2008, sections 38-41 of the office action mailed 07/24/2007. Case law has established that anticipation and operativeness are questions of fact; however, obviousness and enablement are questions of law. See In re Lindell, 155 USPQ 521; In re Chilowsky, 134 USPQ 515. Where the experts have given an opinion as to the ultimate legal conclusion of enablement, to which no weight is given. The underlying basis for the legal conclusion has been considered in this and every office action in the record since the Declarations were submitted.

33. The Journal of Invasive Cardiology, Vol. 17, Jul 01 2005, Issue Number 7, published two discussions among medical experts, one regarding a presentation titled, "Progenitor Cell Transplantation and Function following Myocardial Infarction" (Author unknown) (http://www.invasivecardiology.com/article/4348), the other regarding a presentation by Holmes, "Tissue Engineering and Interventional Cardiology" (http://www.invasivecardiology.com/article/4347). These discussions include the following (emphasis added herein):

a. From "Progenitor Cell Transplantation and Function following Myocardial Infarction" (http://www.invasivecardiology.com/article/4348):

i. **O'Neill** "Do we know yet which would be the most efficient way — **if the appropriate cell were to be found** — to deliver the cells for the most efficient myogenesis?"

ii. **O'Neill**: The problem I have is that the stem cells are very sensitive to hypoxia; **they need an oxygenated environment in order to thrive**. Thus, if these cells are injected into a core infarct area, it will likely be hypoperfused and the ambient oxygen tension in that area may not be sufficient to support those cells… But my question is: Why would those cells stay at that target site? Also, **we are lacking basic scientific understanding** of the signals that allow the stem cells to hone in on that particular tissue.

iii. **Nikol**: "**These findings are not very convincing in my opinion, including the data from the Strauer group** which lacked a truly randomized control group … Also, **there may not be a homogeneous distribution of cells**…"

iv. **Gonschior** , "It would be very smart to just inject the cells intravenously… **In fact, it turned out that endocardial delivery of these cells was the most efficient**"

v. **O'Neill**: "…bone marrow is unfiltered…Basically, the injection contains the "kitchen sink" **and we hope that the right cells go to the right place and do the right thing**.

b. From "Tissue Engineering and Interventional Cardiology", (http://www.invasivecardiology.com/article/4347):

vi. **Dangas**: **When it became clear that we were unable to identify the most appropriate and effective agent for angiogenesis, we looked toward the newly fashionable stem cell-based therapies**. Even researchers make 3 million agents, and 2 of them turn out to be effective, that would be fine. On the other hand, perhaps the stem cells will produce 2 or 3 agents that work for angiogenesis, but at the same time, 1 or 2 other agents produce negative effects — the result being that the positive effect hoped for is not achieved. Thus, the interventional cardiology field must achieve more "crisp" results based on more "crisp" basic science, with better-established findings, in order to better understand what the targets are and pursue them in a more methodological manner. **Our methodology needs to be evidence-based**, as opposed to the focusing on the practicalities of how to achieve our aims. We need to scale down the in vivo applications and return to the laboratory.

vii. **Holmes**: "**We are already in the middle of human trials before obtaining adequate scientific data about which specific cells to use, how many cells, when to deliver them, and how to deliver them**…when these different sorts of cells are delivered intravenously, they go to the lungs and have a "tremendous time," and they don't reach the myocardium. So while it makes perfect sense to use the intravenous approach, these cells are filtered out in the lungs and remain there. If those cells are active and produce cytokines, perhaps that's all we would want to use them for. **Maybe these cells aren't the magic solution, and maybe we don't have a clue about this.** Perhaps we can use these

> cells for the cytokines they produce systemically and they will cause other bone marrow cells to hone in on the site of injury. **But at the present, we just don't know enough about this process**.

34. It is clear that questions of choice of cell, dosing, timing, means of delivery, and cell survival, were still unanswered in these discussions that took place about seven years after the filing of the instant application. Cell therapy is indeed an unpredictable art. The concerns expressed by the participants are the same as those raised herein and in the rejections of record with respect to the lack of guidance provided by the instant specification. Clearly, considerable experimentation had taken place and there was a general agreement that more experimentation was needed. It remains uncertain what the critical cell in the preparations administered in the intervening art is; it may not be any previously characterized stem cell, it may not even be a *stem cell* at all but rather some other previously uncharacterized growth factor secreting cell. This further illustrates that a claim to a method of growing an artery by administering a *stem cell* should be supported by more than a vague enunciation of the concept. Furthermore, all arguments that post-filing successes reported by others were predictable and did not require much experimentation are thoroughly refuted. It is further noted that one of the participants in these discussions was Dr. Richard Heuser, a Declarant of record in the instant case. If Applicant's arguments are to be accepted, then Dr. Heuser, having "read and understood" the instant specification, was in possession of answers to the controversies under discussion. One wonders why Dr. Heuser did not speak up and enlighten his colleagues.

35. It is clear from the discussion above, that many of the critical decisions, manipulation, and preparations take place before the injection is made. Clearly, simply knowing how to inject

cells is not enough to perform a method of growing a new artery. It has been stated repeatedly in the record that the courts have stated that patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute an enabling disclosure. Reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. See *Genentech v. Novo Nordisk A/S* (CAFC) 42 USPQ2d 1001 (1997). While evidence of a fully developed clinical procedure is not required for a patent, the notion that the claimed new result, artery growth, can be achieved using old materials (bone marrow stem cells) and old methods (injection), was indeed "a germ of an idea" at the time the instant application was filed. The instant specification does not even clearly enunciate this germ of an idea, let alone provide an enabling disclosure of how to make and use the claimed invention.

36. It is plausible that cells properly described as "stem cell" (all claims), "stem cell harvested from bone marrow" (claim 407 and dependents) or "stem cells harvested from blood" can cause an artery to grow if they are injected locally at a selected site. However, as stated in Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis." At best, the claims under consideration represent guesses.

The post-filing references of record are not confirmation of the claimed results, but rather they are evidence of further experimentation involved in the act of invention.

37. The rejection of record has given careful consideration to the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the level of skill in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. It has been acknowledged that the level of skill in the art is high. However, the remaining factors indicate that the each of the claims under consideration must be rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Double Patenting

Rejection Maintained

38. Provisional rejection of claims 403-405 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 163 and 170-173 of copending Application No. 10179589 is maintained for reasons of record. Applicant's intent to file a terminal disclaimer upon an indication of allowable subject matter is acknowledged.

Rejection Withdrawn

39. Provisional rejection of Claims 403 and 407-412 under 35 U.S.C. 101 as claiming the same invention as that of claims 161-164 and 172-174 of copending Application No. 10179589 is hereby withdrawn in favor of the following new rejection.

New Rejection

40. Claims 382-406 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of 161-164 and 172-174 copending Application No. 10179589. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

41. The respective independent claims 174 and 403 recite nearly identical methods of producing and integrating an artery at a selected site in a body of a human patient comprising placing a stem cell in a body of a human patient and growing said desired artery. Step (b) of claim 403 recites an additional step of forming a bud. Applicant's intended meaning for step (b) was indicated in remarks filed 11/28/2007 in the instant case: "the only step required by the practitioner is that of injecting stem cells into a selected site in a patient's body. Once injected, the stem cells interact with the human host by differentiating along predetermined physiological developmental pathways to form a vascular bud which grows into an artery." (This explanation has been repeated in Applicant's Brief filed 11/24/2008, p.7). Therefore, Applicant indicates that step (b) inherently occurs every time step (a) is performed. Therefore this limitation does not distinguish the claims. Copending claim 174 requires locally *placing* a stem cell in the body of a human patient while claim 403 requires locally *injecting* stem cells. As placing is broader than injecting, the independent claims are not identical, but are merely obvious variants of one another. Dependent copending claims 161-164, 172 and 173 in this case and instant claims 407-412 add identical limitations to their identical base claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

42. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD., whose telephone number is (571)272-1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571 272 0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/D. C. G./
Examiner, Art Unit 1647

/David S Romeo/
Primary Examiner, Art Unit 1647